Energy expenditure and physical activity in relation to bone mineral density in women with anorexia nervosa.

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Energy expenditure and physical activity in relation to bone mineral density in women with anorexia nervosa

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Objectives: To assess sleeping metabolic rate (SMR), average daily metabolic rate (ADMR), and total bone mineral density (TBMD) in women with anorexia nervosa, and to evaluate the effect of daily physical activity on TBMD.
Design: We compared women with anorexia nervosa and controls using measurements on body composition, and energy expenditure. Relations between these measurements were investigated.
Setting: Daily living environments in The Netherlands, and body composition and energy expenditure laboratory of the Department of Human Biology.
Subjects: Twelve adult, non-hospitalized women with anorexia nervosa, and sixteen adult normal weight women.
Interventions: Average daily metabolic rate was measured with the doubly labeled water method and sleeping metabolic rate in a respiration chamber. TBMD was measured by dual energy X-ray absorptiometry, and percentage body fat was calculated combining the results from underwater weighing and deuterium dilution.
Results: TBMD was significantly lower in anorexia than in controls (0.989 ± 0.081 *vs* 1.144 ± 0.054 g/cm^2). Also ADMR and SMR were reduced in anorexia. The physical activity index (PAI = ADMR/SMR) was not significantly different from PAI in controls. In anorexia, TBMD was related to the PAI ($R^2 = 0.35$, $P < 0.05$). Finally, stepwise multiple regression revealed that PAI together with the study groups as dummy variables could explain 69% of the variation in TBMD.
Conclusion: These findings show that in anorexia TBMD is reduced, but that nonetheless physical activity has a significant positive effect on bone density.
Descriptors: anorexia nervosa; physical activity; doubly labeled water; body composition; dual energy x-ray absorptiometry

Introduction

Many women with anorexia nervosa (AN) have prolonged hypogonadism, which may result in severe and widespread bone loss (Rigotti *et al*, 1984; Biller *et al*, 1989). Apart from negative factors affecting bone mineral density (BMD), as malnutrition, and hormonal disturbances (Rigotti *et al*, 1984; Biller *et al*, 1989), positive factors are physical activity (Aloia *et al*, 1988; Kanders *et al*, 1988), and possibly dietary Ca intake (Halioua & Anderson, 1989; Sowers & Galuska, 1993).

Contrary to the symptoms associated with undernutrition, patients with AN tend to remain energetic, show high activity levels (Casper *et al*, 1991; Pirke *et al*, 1991), and may exercise excessively (Kron *et al*, 1978). Since recovery of bone density in AN is relatively uncommon (Rigotti *et al*, 1991), it is important to know to what extent physical activity and/or exercise may contribute to an improvement of the BMD or at least to a decrease of the net bone resorption. There are indications that in anorexia a high level of physical activity may result in relatively greater bone densities (Rigotti *et al*, 1984; Seeman *et al*, 1992). In these studies physical activity was not measured directly, but assessed by interview or questionaire. We studied the relation between physical activity and bone mineral density in women with prolonged anorexia nervosa. Energy expenditure and physical activity were measured by indirect calorimetry using the doubly labeled water technique and respiration chamber measurements. Bone mineral density was determined by dual X-ray absorptiometry (DXA).

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Methods

Subjects

Twelve adult, non-hospitalized women with anorexia nervosa were selected according to the DSM-III-R criteria for mental disorders (1987). All had a body mass index (BMI) ≤ 18 kg/m^2. The history of anorexia nervosa ranged from 5–28 y. Their body mass had been stable (± 0.5 kg) during the three months prior to the experiment. All women were classified as food restrictors according to the Eating Disorder Inventory (Garner *et al*, 1983). Seven subjects had amenorrhea of >3 months duration. Four subjects used oral contraception. In one subject the uterus was surgically removed. Five subjects were smokers. The control group consisted of 16 adult normal weight women, participating in a study on energy expenditure (Westerterp *et al*, in press). Controls were free of eating disorders and certified to be in good physical health by a staff physician. Three controls were smokers. All subjects signed a written informed consent. The study protocol was in accordance with the University Ethics Committee guidelines.

Calcium intake
Food consumption was obtained from a 7 d dietary record. At their own house the participants were given oral and written instructions on how to fill in records with exact descriptions and amounts of all foods consumed. Ca consumption was calculated by Becel® computer program, software version 1994 (Unilever Research Laboratorium, Vlaardingen, The Netherlands), using the Dutch Food Composition Table (Kommissie UCV, 1994). Ca-intake was corrected under/over reporting, using the ratio energy intake from records divided by energy expenditure from DLW, and body weight changes, assuming 30 MJ/kg weight loss.

Energy expenditure
Sleeping metabolic rate (SMR) was measured in a 14 m^3 respiration chamber (Schoffelen *et al*, 1984) during the night prior to the field measurements. SMR was determined from the O_2 consumption and the CO_2 production according to Weir (Weir, 1949) over a 3h interval between 2:30 h and 7:00 h when the subjects were minimally active (checked with Doppler radar observations).

ADMR was measured over a 14 d period with the doubly labeled water (DLW) method according to the procedures as described by Westerterp *et al*, 1995. At the evening (22:00 h) before the start of the field measurements the subjects drank a weighed amount of ^{18}O and ^{2}H after collection of a baseline urine sample. The excess ^{18}O in urine was approximately 300 ppm and ^{2}H was 150 ppm. Further urine samples were collected from the second and last voiding at day 1, day 8, and day 15. Isotope abundances in the urine samples were measured with an isotope ratio mass spectrometer (VG Isogas, Aqua Sira) and CO_2 production was calculated from isotope ratios in baseline, day 1, day 8 and day 14 samples with the equations from Schoeller *et al*, 1986. All samples were measured in duplicate and the difference between duplicates was < 1 ppm. CO_2 production was converted to average daily metabolic rate (ADMR) using an energy equivalent based on the individual macronutrient composition of the diet, as determined from the dietary records. The ratio between ADMR and SMR was calculated to determine the overall physical activity index in daily life (PAI = ADMR/SMR).

Densitometry
Whole body density was determined by underwater weighing in the fasted state. Lung volume was measured simultaneously with the helium dilution technique using a spirometer (Volugraph 2000, Mijnhardt). To account for possible variation in FFM hydration, the percentage body fat was calculated combining the results from underwater weighing and deuterium dilution using the equations of Siri (Siri, 1956).

Bone mineral density
Total body bone mineral content (TBMC) and bone mineral density (TBMD) were determined for the whole body by a dual X-ray absorptiometer (DPX-L, Lunar Corp., Madison, WI). We used the medium scan speed (80 mm/s) with a resolution of 4.8 × 9.6 mm. Bone mineral content and density were calculated by Lunar software (version 1.3 z). For the whole body scan the subject lies in a supine position. The results were compared to the Germany Total Body White Reference Population provided by the manufacturer. In the control group, bone measurements by DXA have been performed in 11 subjects.

Statistical analyses
Mann–Whitney *U*-test was used to establish significance of any differences between women with anorexia and controls. Differences between predicted and measured values were tested for statistical significance by Wilcoxon signed rank test. Pearson correlation coefficients were used to test associations between variables. Analyses of co-variance (ANCOVA) was used to test for differences in linear relations. Pearson correlation coefficients and stepwise regression analyses were used to determine the relationships between supposed factors related to BMD. All results are expressed as mean values and standard deviation (s.d.).

Results

Subject characteristics
The anorectic subjects were on average significantly older than controls, however age range overlapped to a large extent (Table 1). Anorectics and controls were not different in height, but the women with anorexia had significantly lower body mass and BMI.

Body composition
The percentage body fat was significantly lower in anorexia compared to controls (Table 2). There was a positive correlation between percent fat and BMI ($R^2 = 0.76$, $P < 0.001$). FFM was significantly lower in anorectics. FM- and FFM-indices were lower in anorexia compared to controls. TBMC and TBMD were significantly lower in anorexia. Compared to the German Total Body White Reference population, the women with anorexia had a significantly lower age and weight matched TBMD (95% confidence interval of the mean: 89–99%), while the TBMD of the controls was not significantly different from this reference (95% CI of the mean: 97–104%).

Average body weight change during the DLW measurement period was -0.20 ± 0.45 kg in the anorectics and in controls 0.18 ± 0.65 kg.

Energy metabolism
Both SMR and ADMR were significantly lower in anorectic women (Table 3). The data from anorectics and controls together revealed significant relations between ADMR and SMR with FFM (ADMR = 0.32 FFM − 3.40, $r^2 = 0.71$, $P < 0.001$; SMR = 0.16 FFM − 0.98, $r^2 = 0.77$, $P < 0.001$). Since there is very little overlap in FFM between the two groups, the data were treated separately: in the

Table 1 Physical characteristics of women with anorexia nervosa and controls

	Anorexia (n = 12)			*Controls (n = 16)*			*Mann–Whitney-U*
Variable	*mean*	*s.d.*	*range*	*mean*	*s.d.*	*range*	*P*
Age (y)	34.3	8.4	21–46	25.9	5.1	20–35	< 0.01
Body mass (kg)	45.5	4.7	38.3–54.6	65.6	7.7	53.6–79.6	< 0.001
Height (m)	1.66	0.06	1.56–1.75	1.66	0.06	1.56–1.75	not significant
BMI (kg/m^2)	16.5	1.7	12.5–18.2	23.7	2.1	19.3–27.9	< 0.001

Table 2 Body composition of women with anorexia nervosa and controls[a]

	Anorexia (n = 12)			*Controls (n = 16, TBMD: n = 11)*			*Mann–Whitney-U*
Variable	*mean*	*s.d.*	*range*	*mean*	*s.d.*	*range*	*P*
Body fat (%)	21.3	5.6	9.6–28.2	31.9	6.1	19.5–41.8	< 0.005
FFM (kg)	35.7	2.4	32.3–40.2	44.4	3.9	37.8–50.2	< 0.0001
FM-index (kg/m^2)	3.6	1.1	1.2–5.1	7.7	2.0	3.8–11.0	< 0.0001
FFM-index (kg/m^2)	13.0	1.1	11.3–14.7	16.1	0.7	15.0–17.8	< 0.0001
TBMC (kg)	1.90	0.25	1.34–2.19	2.50	0.28	2.15–3.04	< 0.0001
TBMD (g/cm^2)	0.989	0.081	0.856–1.129	1.144	0.054	1.081–1.276	< 0.0005

[a]FFM, fat free mass; TBMC, total bone mineral content; TBMD, total bone mineral density.

Table 3 Energy metabolism of women with anorexia nervosa and controls[a]

	Anorexia (n = 12)			*Controls (n = 16)*			*Mann–Whitney-U*
Variable	*mean*	*s.d.*	*range*	*mean*	*s.d.*	*range*	*P*
SMR (MJ/24 h)	4.51	0.55	3.62–5.36	6.23	0.45	5.55–6.85	< 0.0001
ADMR (MJ/24 h)	7.61	1.31	4.72–9.77	10.9	1.2	7.9–12.6	< 0.0001
PAI	1.70	0.30	1.07–2.10	1.75	0.15	1.38–2.03	not significant

[a]RMR, resting metabolic rate; ADMR, average daily metabolic rate; PAI, physical activity index (ADMR/SMR); s.d., standard deviation.

anorectics only SMR was related to FFM (SMR = 0.16 FFM − 1.23, $r^2 = 0.51$, $P < 0.01$). In the controls both ADMR and SMR were related to FFM (Figure 1). ADMR in anorectic women is low relative to controls: only one out of twelve measurements was above the regression line of the controls, while all the others were below this line. The same holds for the SMR. SMR in relation to FFM was significantly lower in anorectics (Test of slopes: $F(1,25) = 3.96$, ANCOVA: $F(1,26) = 15.6$).

The results from PAI showed one outlier with an extremely low value (PAI 1.07). Removing this value revealed a mean PAI of 1.77 ± 0.21 ($n = 11$). With or without the outlier the PAI was not significantly different between anorexia and controls.

Determinants of bone density

Combined data from anorexia and controls showed that total bone mineral density was negatively related to age (Figure 2a), and positively to body mass index (Figure 2b). Daily Ca-intake in the women with anorexia was 973 ± 433 mg/d, and 1102 ± 461 mg/d in the controls. There was no relation between TBMD and Ca intake. TBMD in anorexia was related to the PAI (Figure 2c). Taking the data from anorexia and controls together there was no relation. TBMD was in general higher in controls than in anorexia with comparable PAI (Figure 2c). There was no significant relation between TBMD and PAI for controls only, which can at least in part be explained by the small range in PAI in these subjects.

Including the two study groups as dummy varaibles (SG), a stepwise regressions between the independent variables Ca intake, age, BMI, SG, and PAI and the dependent variable TBMD revealed that TBMD was significantly related to PAI and SG:

TBMD = 0.15 PAI + 0.148 SG + 0.732 ($R^2 = 0.69$, $P < 0.001$).

Discussion

Physical activity was measured in women with prolonged anorexia nervosa by determining ADMR by the DLW method and SMR in a respiration chamber.

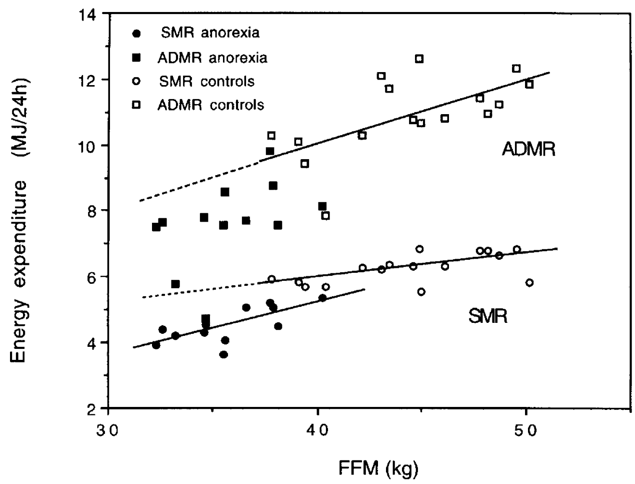

Figure 1 Average daily metabolic rate (ADMR) and sleeping metabolic rate (SMR) plotted against fat free mass (FFM). Anorexia: ADMR: not significant; SMR = 0.16*FFM* 1.23, $r^2 = 0.51$, $P < 0.01$. Controls: ADMR = 0.19 FFM + 2.28, $r^2 = 0.40$, $P < 0.01$; SMR = 0.068 FFM + 3.21, $r^2 = 0.35$, $P < 0.05$

This study shows for the first time in anorexia nervosa a relation between bone mineral density and physical activity. Moreover stepwise regression shows that the variation in TBMD can be explained for 69% by PAI and study group.

Body composition

Body mass, BMI and the percentage body fat were lower in anorexia than in controls. Also the FM and the FM-index were lower in anorexia. This is in agreement with many other studies that find low fat percentages of anorexia compared to controls (Casper *et al*, 1991; Platte *et al*, 1994).

Absolute fat percentage in fact is unexpectedly high (mean 21.3%, maximum 28%), despite low BMI. This means that relative to their body height FFM is low, indicating low nutritional status. This comes up to the conclusions from earlier studies (Mitchell & Truswell, 1987; Hannan *et al*, 1995; Probst *et al*, 1996) that BMI is not a good predictor of body fat in anorexia. Our study

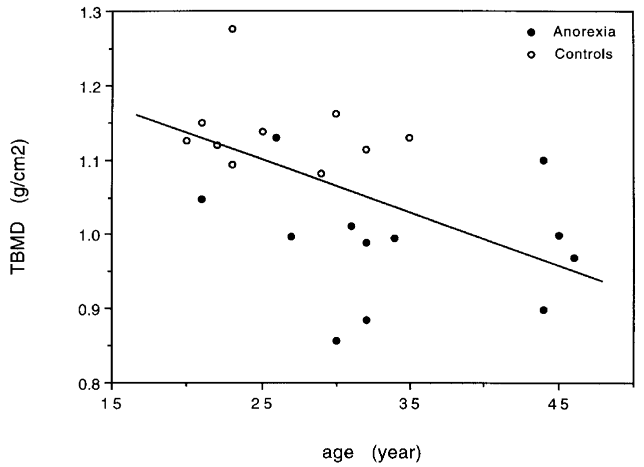

Figure 2a Total bone mineral density (TBMD) plotted against age. TBMD= 0.006 AGE + 1.257, $r^2 = 0.25, P < 0.05$.

indicates that this may especially be the case in women

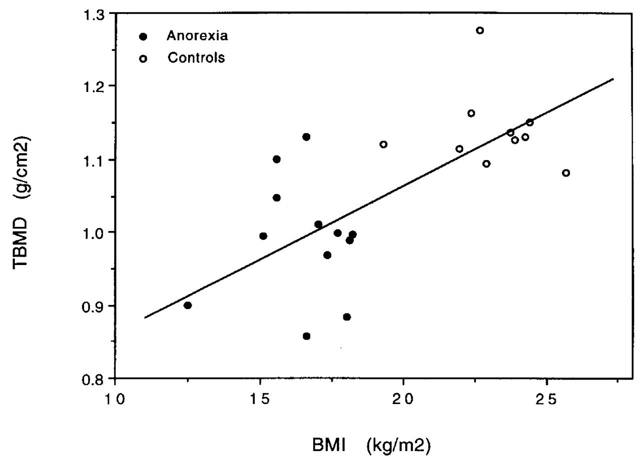

Figure 2b Total bone mineral density (TBMD) plotted against body mass index (BMI). TBMD = 0.019 BMI + 0.692, $r^2 = 0.46, P < 0.001$.

with a long history of anorexia nervosa.

Comparison with others studies is limited since no

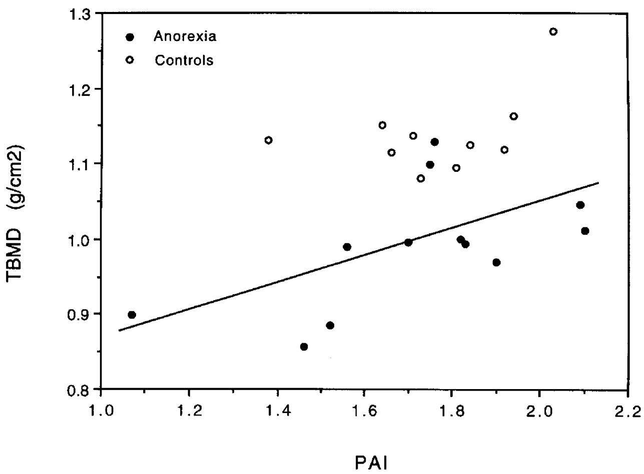

Figure 2c Total bone mineral density (TBMD) plotted against physical activity index (PAI = ADMR/SMR). In anorexia: TBMD = 0.168 PAI + 0.701, $r^2 = 0.35$, $P < 0.05$.

studies account for variation in the hydration of FFM by using the combination of underwater weighing and deuterium dilution. Casper (Casper *et al*, 1991) using ^{18}O-dilution also found some high body fat percentages in anorexia (mean: 16.1%, maximum: 26.7%, $n = 6$).

Energy expenditure

Our study shows that SMR is reduced in anorexia. In most studies RMR is measured. At our laboratory SMR is maximal 5% lower than RMR (measured by ventilated hood under resting and fasting conditions). RMR has often been studied in anorexia and was found to be lower compared to controls (Vaisman *et al*, 1988; Melchior *et al*, 1989; Casper *et al*, 1991; Westerterp *et al*, 1991; Scalfi *et al*, 1993; Obarzanek *et al*, 1994; Platte *et al*, 1994). The decrease in RMR (or SMR) could be the result of a reduction in FFM or of a decrease in energy expended relative to FFM. Our results confirm those of Melchior *et al*, 1989 and Casper *et al*, 1991 in that RMR in anorectics is low per unit FFM. However, it has also been found that RMR per kilogram lean body mass was not significantly different from that of healthy volunteers (Westerterp *et al*, 1991; Obarzanek *et al*, 1994). All studies mentioned here express RMR per unit FFM (or LBM). This is methodologically not correct (Allison *et al*, 1995). When comparing RMR (or SMR) between two populations the relations between RMR (or SMR) and FFM should be compared, using ANOVA statistical analyses. Our study shows that SMR in relation to FFM is reduced in anorexia compared with healthy controls (Figure 1).

ADMR was significantly lower in anorexia compared to the control group, as has been shown before (Casper *et al*, 1991; Pirke *et al*, 1991; Westerterp *et al*, 1991; Platte *et al*, 1994). PAI in anorexia did not differ significantly from PAI of controls. This can be explained by the fact that the absolute values of SMR and ADMR both are reduced in anorexia. This is in contrast to the finding of Casper *et al*, 1991, who found significantly higher PAI in anorexia. From our study group it appeared that although PAI group averages were similar to controls, the women with anorexia had either a low or a high level of physical activity (see also Bouten *et al*, 1996), whereas the controls had a moderate level of physical activity. The wider variability of the PAI in the anorexia group may also explain the lack of relationship between ADMR and FFM.

Factors affecting bone mineral density

It is well confirmed that women with chronic anorexia nervosa develop osteoporosis (Rigotti *et al*, 1984; Bachrach *et al*, 1990; Mazess *et al*, 1990; Seeman *et al*, 1992). Indeed, in this study total bone mineral density was significantly lower in anorexia compared to the control group. Individual values of the women with anorexia were as low as 82% compared to the manufacturers reference populations. Negative factors determining bone density are: undernutrition, hypogonadism, low Ca intake, a low physical activity, and age. Positive factors determining bone density are: a high physical activity, body and/or fat-free weight, and possibly contraceptives (oestrogens). The results from simple regression analyses show that indeed TBMD is significantly negatively related to age, and positively to BMI and PAI. There was no relation with Ca-intake. Multiple stepwise regression shows that 69% of the variation in TBMD can be explained by PAI and study group.

The use of PAI has the problem of scaling as also shown for body composition analyses (Allison *et al*, 1995; Prentice *et al*, 1996). To avoid the problem with scaling, we compared the residuals of the relation between ADMR and SMR with the residuals of the relation between TBMC and BM. The residuals of TBMC are significantly related with the residuals of ADMR ($R^2 = 0.17$, $P = 0.05$). Without one significant outlyer: Residual of TBMC = 0.122 (residual of ADMR) - 0.025, $R^2 = 0.25$, $P < 0.02$. Residual analyses of both anoretics and controls thus demonstrates that the variation in TBMC can be explained for 25% by differences in physical activity.

Age and Ca-intake do not reveal a significant contribution in the multiple regression. Age does not have a significant contribution, probably because the influence of age is small before the age of menopause. The fact that Ca-intake did not have a significant contribution may be caused by the short time interval of Ca-intake measurement (7 d dietary record). Some studies do not show a relation between BMD and Ca-intake (Kanders *et al*, 1988; McCulloch *et al*, 1990; Marken Lichtenbelt *et al*, 1995), while others have found an effect of Ca-intake on BMD (Halioua & Anderson, 1989) or bone mass gain (Recker *et al*, 1992). A possible explanation for those studies that do not find an association between Ca-intake and bone density, may be a Ca-intake above the threshold of 800–1000 mg/d (Kanders *et al*, 1988). In our study there were only three subjects that consumed less than 800 mg/d.

The present study showed that, despite low FFM in women with prolonged anorexia nervosa, both sleeping metabolic rate and average metabolic rate in relation to FFM are low compared to healthy female subjects. Average total bone mineral density is reduced compared to controls and to a reference population. The variation in TBMD can be explained for 69% by physical activity (PAI) and study group. The small sample size and the high age of the anorexic group have to be taken into consideration prior to extend these conclusions to the entire population of women suffering from anorexia nervosa.

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